FSTC-HT-23-1039-68

# U.S. ARMY FOREIGN SCIENCE AND TECHNOLOGY CENTER

DEVELOPMENT OF LIVE VACCINES IN THE SOVIET UNION:

A REVIEW

COUNTRY: USSR

## TECHNICAL TRANSLATION



12)

TECHNICAL TRANSLATION

FSTC-HT-23-1039-68

# DEVELOPMENT OF LIVE VACCINES IN THE SOVIET UNION: A REVIEW

by
A. T. Kravchenko and R. A. Saltykov

SOURCE: ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII, I IMMUNOBIOLOGII
(Journal of Microbiology, Epidemiology, and Immunobiology)
No. 10, pp. 98-102, 1968
USSR

Translated for FSTC by Techtran Corporation

# DEVELOPMENT OF LIVE VACCINES IN THE SOVIET UNION: A REVIEW

## REPORT II

### Virus and Rickettsial Live Vaccine

Interest in live vaccines has always been high in Russia. Thus, only 5 years after E. Jenner's initial experiments, 200,000 persons were inoculated against smallpox in Russia. Only one year after Pasteur's experiments in treating rabies with live, preserved viruses, produced by N. F. Gamalée, the production and use of this preparation was under way at Odessa.

Following the Great October Socialist Revolution, the young Soviet republic was compelled to devote particular attention to the eradication of widespread infectious diseases, including smallpox. Compulsory vaccination of the entire population was introduced by a decree of the Soviet of People's Commissars on April 10, 1919 and by an order of the Council of the National Committee in 1924. An enormous debt is owed the famous Soviet scientists N. F. Gamalée and M. A. Morozov for the organization of the vaccination program in the first years of Soviet power. The efforts of these scientists and their assistants in the years that followed made it possible to achieve a sharp decrease in the morbidity rate for smallpox; by 1938, this disease had been wiped out in the territory of the Soviet Union.

Along with the development of the production capability required to achieve nationwide vaccination, scientific research efforts were directed toward improving the quality of the smallpox vaccine itself. Studies were devoted to increasing the virulence of the smallpox vaccine, ensuring a high degree of viability, and increasing the resistance of the vaccine to the effects of unfavorable external factors.

Using the plasticity of the virus of the smallpox vaccine, Soviet scientists cultured it in various types of animals and obtained several varieties of this virus: variolovaccine, azinovaccine, and azine-ovine vaccine, as well as equine, porcine, lepine and neurolepine vaccines and ovovaccine (Morozov and Korol'kova, 1960).

In the course of a detailed study of the varieties (strains) smallpox vaccine, obtained as the result of prolonged culturing by many methods and in many types of animals, it was found that these strains (varieties) differ in a number of ways (Solov'yev and Mastyukova, 1961; Kiselev and Kozhevnikov, 1961; Yaroslavskaya and Gryaznova, 1965; Bardina et al., 1965; Fedorova, 1965; Nesmeyanova, 1965; Marennikova, 1966). These researchers found that the infectious properties of the developed strains were increased by culturing the smallpox vaccine in various types of animals. Following injection of such vaccines into human subjects, the body temperature of the latter rose above the permissible norm; additional pock marks appeared, and a general rash broke out (Yaroslavskaya, 1965). On the other hand, the infectious properties of the derivative strains decreased as the result of prolonged cultivation by one method (calf-to-calf or chicken embryos) (Morozov and Korol'kova, 1960; Solov'yev and Matstyukova, 1961).

Strains which have been cultivated only in calves (the strain of the Byelorussian Institute of Epideniology and Microbiology, and the EM-63 strain, with high viability and low reactivity) have been recommended for production purposes in the Soviet Union by the Control Institute imeni Tarasevich. In order to ensure a wide program of inoculation on a nationwide scale, adequate stabilization of this preparation was required. Many studies were devoted to this aspect of the problem, and a number of methods were proposed for drying the smallpox vaccine with various "fillers": sucrose and gelatine were tried (Morozov and Korol'kova, 1960); in 1963, on the recommendation of the World Health Organization, peptone was used as a stabilizer for smallpox vaccine.

The efforts of a group of scientists at the Moscow Scientific Research Institute of Virus Preparations led to the development of methods for producing smallpox vaccine in accordance with the recommendation of experts from the WHO; in 1964, all institutes producing smallpox vaccine in the USSR adopted these methods.

The smallpox vaccine developed in the Soviet Union in 1967 was equal to the best forms of this preparation made in other countries in terms of its characteristics.

The basic principles of protection against rabies were developed, as we know, by Pasteur at the end of the last century. In 1886 the Odessa Anti-Rabies Station received from Pasteur the brain of a rabbit, constituting the 115th passage of a preserved rabies virus. Twenty-six anti-rabies stations had been organized in Russia before the 1917 Revolution. The director of the first anti-rabies station was the honorary Academician, N. F. Gamalée. The method proposed by Pasteur for preparing the vaccine was intended for use only at the station itself, so that the need for vaccine in remote regions of the country could be satisfied only by organizing new stations. As of 1927, 72 Pasteur-type stations had been established in the USSR (Dubrovinskiy, 1936). At the same time, methods of preparing the anti-rabies vaccine, proposed by Fermi and Philips, were spreading. These methods made it possible to preserve an emulsion of the brain of a rabbit infected with a preserved rabies virus, as well as to regulate the dosage of the vaccine more precisely. Such a preparation withstood transportation over long distances and made it possible to organize Pasteur-type inoculation centers. Thus, 633 such centers were in operation by 1935. In addition, the availability of anti-rabies vaccine preserved with phenol (15) or glycerine made it possible to concentrate its production in several well-equipped installations. In 1967, anti-rabines vaccine was being made at only 10 institutions in the USSR, which satisfied the needs of the entire nation for this preparation.

The results of using various forms of anti-rabies vaccine for over 80 years allow us to judge this preparation to be highly effective and still the only one which is reliable for treating human beings attacked by rabid animals. In addition, from the very first years of using the vaccine (Gamalée, 1947) to the present, arguments have been waged over the danger to human beings from the live preserved virus. In several countries, including the USSR (Voroshilova and Itselis, 1958; Gaydamovich, 1958), detailed studies have been made of cases where persons died following the injection of anti-rabies vaccine containing the live preserved virus. A conclusive indicator of its etiological role in many cases of serious complications was the fact that the animals which attacked the victims remained healthy, while large amounts of virus (identical in nature to the preserved virus) were taken from the brains of the dead persons. It was determined experimentally that the brain tissue of new-born animals (unlike that of adults) does not cause the development of allergic encephalomyelitis in guinea pigs. Using this as a basis, Svet-Moldavskiy (1960) developed the "non-allergenic anti-rabies cine", hailed by medical science in 1964. According to data from the Control Institute imeni Tarasevich (1967), practical use of vaccine made from the brains of new-born rats by the Fermi method does not differ in its ability to produce complications in the inoculated persons from vaccine made by the same method from the brain tissue of sheep and rabbits.

A new vaccine, made from preserved rabies virus of the "Sad" variety, has recently been recommended for testing in the USSR; it is obtained from a culture of kidney cells of the Syrian hamster (Selimov, 1966). This vaccine does not contain proteins from the animals' brain tissue.

Despite the numerous points of dispute among scientists, the fact remains unquestioned that under certain circumstances, the preserved virus can produce the disease in a human patient, with fatal consequences. It is possible that this is determined by the method in which the vaccine is used (repeated injection at short intervals).

Portection of the patient against infection with influenza and similar ailments is a very complex problem which still cannot be considered solved. The only scientifically approved method of prophylaxis against influenza at the present time is mass immunization. Soon after discovery of the agent which causes influenza (1935), two methods were found for specific protection from this infection, involving use of killed and live vaccines. Soviet scientists began developing prophylactic preparations using the live virus.

The first live vaccine against influenza was proposed by Smorodintsev in 1937. The epidemic virus of influenza was adapted to the organism of the mouse. The live liquid vaccine was prepared from the tissues of mice which had been infected with the said virus. This vaccine did not receive wide distribution.

More detailed studies of the pathogenesis and immunity mechanism in influenza, conducted by a large collective of Soviet investigators led by V. D. Solov'yev, M. I. Sokolov (1954, 1960) and A. A. Smorodintsev (1961) made it possible to prepare the vaccine on growing chicken embryos from strains of the virus which had been cultivated in the human organism or adapted to human tissue by culturing them in vitro. These vaccines were obtained in the form of dry preparations. Methods were devised for stabilizing the live influenza vaccine and prolonging its useful life (Sokolov, 1960; Parizh, 1965). Rational methods were developed for using the vaccine against influenza by introducing it through the nose into the respiratory passages.

A network of laboratories was organized in the Soviet Union under the direction of the Institute of Virusology of the Academy of Medical Sciences of the USSR; their task was to determine the level of immunity of the population against influenza and to isolate the strains of this virus.

The studies conducted at the Central Institute imeni Tarasevich determined the guidelines for making a preliminary selection of strains intended for making vaccine (Kolchurina, 1965). Criteria were also established for the reactivity of live influenza vaccine, making it possible to use it for widespread immunization of human beings. The live

vaccine, effective against influenza and suitable for vaccinating adults, produces a much greater percentage of general reactions (Ritova, 1956). Consequently, a vaccine can be prepared (for immunizing children) from strains which have been subjected to further attenuation (Smorodintsev et al., 1966).

The quality of the live vaccine for use against influenza is determined not only by the characteristics of the vaccine strains, but also by the coincidence of their antigen structure with that of the influenza virus which causes epidemics.

Serious concern was caused by the propagation of the polio-myelitis virus in many countries of the world, which was observed during World War II and the years immediately afterward. Attempts to solve this problem by using killed vaccines did not yield positive results, since these preparations, which protected immunized persons from the disease and particularly from the serious consequences of polio, did not prevent the growth of the pathogenic virus in the cells of the intestine and its circulation among the population (Chumakov and Voroshilova, 1966). The solution to the complex problem of immunoprophylaxis of poliomyelitis in the Soviet Union demanded the services of an immense number of scientific researchers and practicing physicials. Particularly important was the success achieved through the work of a collective of scientists led by M. P. Chumakova in Moscow and A. A. Smorodintsev in Leningrad. From among the large collective of participants in this work, we should also mention the following scientists who so successfully carried out the various aspects of the program: virusological studies - M. K. Voroshilova, A. I. Drobyshevskaya; organization of mass production of live vaccine - V. A. Lashkevich; evaluation of the quality of the resultant vaccine - S. G. Dzagurov; determination of the effectiveness of the vaccination - S. G. Drozdov.

Particular success marked the solution of the problem of the method of administering the vaccine in the form of candy-coated tablets (Chumakov). In 1967, the live vaccine was used in the USSR against poliomyelitis, both in the liquid form and in the form of candy-coated tablets consisting of a mixture of 3 serological types.

The strains of vaccine used in producing the polio vaccine are kept under the constant supervision of the Control Institute imeni Tarasevich. Careful observations, conducted over a period of about 10 years, indicate that the characteristics of these strains remain sufficiently stable.

In the Soviet Union, a group of scientists under the direction of P. V. Smirnov (1940) and later P. G. Sergiyev et al. (1956) made attempts to prepare live vaccines against measles but did not meet with noticeable success. Following publication of the work of Enders et al., who isolated the measles virus in a tissue culture and developed the principle of obtaining strains of the vaccine, studies on obtaining live vaccines against measles became more successful.

As of the present time, several live vaccines have been suggested for use against measles. Thus, a live vaccine was obtained from the USSR5B strain (Zhdanov and Fadeyeva, 1959; Fadayeva, 1966). The vaccine was isolated from the blood of a measles patient in 1958 and cultured in human amnionic cells, after which it was transferred to the tissues of chicken embryos. In a test on human subjects, the vaccine was found to be non-reactogenic but non-immunogenic (Zhdanov et al., 1960). Later, another vaccine from the Leningrad 4 (L4) strain was proposed; it was isolated in 1958 from the throat of a measles patient and cultured in human kidney cells (Boychuk et al., 1965; Smorodintsev et al., 1966). This vaccine produced a clinically pronounced process in the majority of children who were given it. Its use in practice was possible only with the simultaneous administration of anti-measles gamma globulin. A vaccine was also obtained from the Leningrad 16 (L16) strain, isolated from a patient (Taros, 1963; Smorodintsev et al., 1965; Kolchurina, 1965) on kidney-cell tissue cultures from guinea pigs, and then grown on this tissue. A test of the measles vaccine of the L16 strain (Smorodintsev et al., 1965; Taros et al., 1965) on humans showed its limited reactivity (without the use of gamma globulin) and high immunogenic power. The Control Institute imeni Tarasevich has recommended the L16 strain for widespread use.

Finally, a live vaccine of the Enders-Schwartz-Chumakov (ESC) strain was obtained from a variety of the Enders-Schwartz strain by culturing it primarily in kidney cells from the golden marmoset. In epidemiological tests, the live cortical vaccine of the ESC strain was found to have low reactivity, while the percentage of seroconversions reached nearly 100 (Chumakov, 1967).

Attempts at specific prophylaxis of epidemic parotitis with killed vaccines proved less effective. Greater success was obtained with experiments in developing a live vaccine against parotitis.

A group of scientific workers at the Leningrad Institute of Epidemiology and Microbiology imeni Pasteur developed an original live vaccine against parotitis (A. A. Smordintsev and Klyachko, 1954). Prolonged culturing of the agent causing parotitis, which is pathogenic for man, in developing chicken embryos carries with it a gradual decrease in its pathogenic properties. The preparation suggested for use contains a mixture of several strains of vaccine virus of parotitis after various periods of culturing in chicken embryos. A broad test of the reactivity and effectiveness of live parotitis vaccine (Klyachko, 1958; Klyachko and Shaposhnikova, 1965; Shaposhnikova, 1965; Raykhstad et al., 1965) showed that the vaccine has a low reactivity, is effective, and is able to confer prolonged immunity.

Specific protection against rickettsiosis and especially against exanthematic typhus has occupied the attention of scientists since the first days of Soviet power.

A live vaccine against exanthematic typhus has been developed at the Institute of Microbiology and Epidemiology imeni Gamelée of the Academy of Medical Sciences of the USSR under the direction of I. F. Zdrodovskiy (1957, 1959) and at the Perm Institute of Vaccines and Sera under the direction of A. V. Pahenichnov (1963). Detailed studies were made of the quality of the "E" strain, isolated by the Spanish scientists Clavero and Perets-Golardo in 1943 from the blood of a patient and made apathogenic for man after 255 passages in developing chicken embryos. The scientists at the Perm Institute of Vaccines and Sera obtained an original variety of the apathogenic strain of the agent causing exanthematic typhus 5/66. When live vaccine of the "E" strain is administered to patients, it confers simple immunity, but in a certain number of those inoculated, especially persons of advanced age, a serious reaction takes place (Pshenichkov et al., 1959; Mrakov et al., 1963).

In recent years, interesting data have been obtained on the immunizing properties of certain antigen fractions, isolated from the agent causing exanthematic typhus (Golinevich and Voronova, 1966). On the basis of these studies by the Institute of Microbiology and Epidemiology imeni Gamalee of the Academy of Medical Sciences of the USSR, a dried live combined exanthematic-typhus vaccine, Type "E" (dried ZhKSV-Ye) was developed and used in 1964, which consists of a mixture of ether lysate of the pathogenic strain of rickettsiae of Provachek and vaccine strain "E". The combined vaccine confers high immunity and insignificant reactivity (Yablonskaya, 1964; Yablonskaya et al., 1967). An ether lysate of the pathogenic strain, when given simultaneously with strain "E", protects the organism from severe delayed reactions.

The killed vaccine against Q-fever (Khodukin et al., 1954; Yasil'-yeva and Yablonskaya, 1955) has shown a high reactivity when administered to human beings. Particular discomfort was caused by cold sores which appeared on the vaccinated persons after the second and third injections (Fedorova et al., 1958; Kulagin et al., 1958). Such a vaccine cannot be used for practical treatment.

In the laboratory of P. F. Zdrodovskiy, who was studying the characteristics of strains of agents causing Q-fever which had been cultured in growing chicken embryos, a strain was discovered which is apathogenic for guinea pigs (Genig, 1960) and which was called the "M" variety of the virulent strain of Grit Q-fever. In addition, a live vaccine was prepared from this apathogenic strain of Q-fever (Zdorovskiy, Genig, 1962) which was accepted for use in medical practice in 1964 according to Interrepublic Technical Specification No. 42. This vaccine confers immunity following a single injection in man, and has insignificant reactivity (Genig et al., 1965).

There is considerable theoretical and practical interest regarding the direction of the studies undertaken under the leadership of P. F. Zdrodovskiy on the development of so-called live chemo-vaccines (Kekcheyev, 1966). The essence of the author's many years of study is that the virulent strains of various forms of rickettsiae, when mixed with a certain amount of antibiotics, lose their ability to produce clinically developed disease in animals and man, but they retain simple immunity. The author has developed and tested in experiments on human subjects, live chemo-vaccines from the agents producing rat rickettsiosis, Q-fevers, tick-carried exanthematic typhus, and Tsutsugami fever.

The history of the specific prophylaxis against infectious diseases produced by viruses and rickettsiae, shows that only live vaccines can both ensure a reliable protection against the virulent agents of infection and prevent their circulation among the population. Live vaccines, unlike killed ones, can be used once and can be given both subcutaneously and supercutaneously (smallpox)., by way of the respiratory passages (influenza), or orally (polio). They are at least reactogenic, since they are given in small doses. Increasing the dose of live vaccine even 100 times has no effect on the development of the clinically pronounced specific process. Live vaccines are more suitable from the economic point of view than are killed ones; all else being equal, it is easier to obtain them in quantities sufficient to ensure that all who need it will be protected against infection.

Vaccine strains of viruses and rickettsiae are difficult to obtain, since there are as yet no definite methods based on modern genetics which could make it possible to obtain strains of vaccine with the properties determined in advance. The strains of vaccine which are used in practice require constant careful supervision and detailed testing of their properties, since prolonged culturing in laboratory conditions, as a rule, tends to change their characteristics.

When certain live vaccines are introduced into the organism through the point of entry of the infection (polio, influenza), there is often interference with the viruses that causes damage to the susceptible cells, so that in order to confer immunity to a relatively large group of persons (polio, influenza), the vaccine must be given in several doses. The anti-virus and rickettsial live vaccines are incubated in cultures of cells of different animals or developing chicken embryos, which, as a rule, are not free of various forms of viruses. The methods of obtaining live virus and rickettsial vaccines that are free of virus contaminants is very difficult.

The vaccine strains of viruses and rickettsiae which are widely employed were obtained by changing the nutrient medium of the agent, which had been prepared, as a rule, empirically. In order to have a more successf l and wider application of live vaccines in the struggle against the numerous infectious diseases of virusial and rickettsial etiology, it will be necessary to develop methods of controlled production of new, highly effective vaccine strains, based on the achievements of modern genetics. We must establish guidelines which will determine the suitability of new vaccine strains for use in preparing live vaccines, and we must perfect the present methods of stabilizing the biological properties of vaccine strains and the activity of live vaccines.

UNCLASSIFIED
Security Classification

**DOCUMENT CONTROL DATA - R & D**

*(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)*

1. ORIGINATING ACTIVITY (Corporate author)
Foreign Science and Technology Center
US Army Materiel Command
Department of the Army

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP

3. REPORT TITLE
Development of Live Vaccines in the Soviet Union: A Review

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)
Translation

5. AUTHOR(S) (First name, middle initial, last name)
A. T. Kravchenko and R. A Saltykov

| 6. REPORT DATE | 7a. TOTAL NO. OF PAGES | 7b. NO. OF REFS |
|---|---|---|
| APR 1 1969 | 9 | N/A |

8a. CONTRACT OR GRANT NO.

b. PROJECT NO. 99030600 0301

c. 9223628 2301

d.

9a. ORIGINATOR'S REPORT NUMBER(S)
FSTC-HT-23-1039-68

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
ACSI Control Number (None)

10. DISTRIBUTION STATEMENT
Distribution of this document is unlimited.

11. SUPPLEMENTARY NOTES

12. SPONSORING MILITARY ACTIVITY
US Army Foreign Science and Technology Center

13. ABSTRACT

The author presents a survey describing the history of the development and use of live and killed viruses and rick ettsiae in the Soviet Union to combat such infectious diseases as measles, typhus, polio and influenza. The methods of obtaining vaccines through tissue culture are described, and the need to improve the quality of such vaccines is emphasized.

DD Form 1 NOV 68 1473 SUPERSEDES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

UNCLASSIFIED
Security Classification

| 14. KEY WORDS | LINK A | | LINK B | | LINK C | |
|---|---|---|---|---|---|---|
| | ROLE | WT | ROLE | WT | ROLE | WT |
| Vaccine, immunology | | | | | | |